Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 2, 37 and 53 are pending in the application, with claims 1, 37 and 53 being the independent claims. Claim 38 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1 and 37 are sought to be amended. These amendments have been made to place the claims in condition for allowance and/or in better form for consideration on appeal. *See* 37 C.F.R. § 1.116(b). These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Information Disclosure Statements

Eight separate Information Disclosure Statements have been filed in the above-referenced patent application. The dates on which these IDSs were filed in the U.S. Patent and Trademark Office are as follows:

- Information Disclosure Statement, January 18, 2000;
- First Supplemental IDS, March 14, 2000;
- Second Supplemental IDS, August 14, 2000;
- Third Supplemental IDS, November 30, 2000;

- Fourth Supplemental IDS, December 27, 2000;
- Fifth Supplemental IDS, January 16, 2001;
- Sixth Supplemental IDS, February 15, 2001; and
- Seventh Supplemental IDS, May 9, 2003.

The Examiner noted that the references cited in the IDSs of January 16, 2001 and February 15, 2001 have been considered and signed by the Examiner. (*See* Paper No. 24, page 3.) The Examiner indicated, however, that the publications listed on the IDSs of January 18, 2000, March 14, 2000, and December 27, 2000 could not be located, and that the documents cited in the IDSs of August 14, 2000 and November 30, 2000 have been located but the PTO Forms-1449 for these IDSs must be re-submitted. (*See* Paper No. 24, page 3.)

As a courtesy, Applicants submitted the following documents directly to the Examiner on October 2, 2003:

- Copy of IDS, filed January 18, 2000;
- PTO 1449, filed January 18, 2000 (33 pages);
- Copies of the one hundred eighty six (186) documents listed on the PTO-1449 filed January 18, 2000;
- Copy of First Supplemental IDS, filed March 14, 2000;
- PTO-1449, filed March 14, 2000 (2 pages);
- Copies of the three (3) documents listed on the PTO-1449 filed March 14, 2000;
- Copy of Second Supplemental IDS, filed August 14, 2000;
- PTO-1449, filed August 14, 2000 (5 pages);

- Copy of Third Supplemental IDS, filed November 30, 2000;
- PTO-1449, filed November 30, 2000 (1 page);
- Copy of Fourth Supplemental IDS, filed December 27, 2000;
- PTO-1449, filed December 27, 2000 (1 page); and
- Copies of the five (5) documents listed on the PTO-1449, filed December 27, 2000.

Applicants respectfully ask the Examiner to consider all of the submitted documents and to make the same of record in the prosecution of this patent application.

II. Claim Objection

Claim 38 was objected to as being dependent upon a rejected base claim. (*See* Paper No. 24, page 4.) Applicants have added the limitation of claim 38 to claim 37 and have cancelled claim 38. Therefore the objection to claim 38 is moot and should be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-2 and 37-38 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (*See* Paper No. 24, page 4.) Applicants respectfully traverse this rejection.

Applicants maintain that the methods and compositions of the present application are fully enabled. The present inventors have demonstrated that metal chelators, including

bathocuproine, promote the solubilization of Aβ from human brain homogenates. (*See* Specification at page 91, line 18 through page 94, line 25.) The inventors also discovered the relationship that exists between dose of chelator used and the extent to which Aβ is resolubilized. (*See S*pecification at page 94, lines 7-25.) With regard to bathocuproine in particular, it was discovered that there is a clear dose-dependent increase in Aβ extraction from human brain. (*See id.* at page 94, lines 22-25 and Figure 19E.) The inventors also found that, as with human brain, homogenates of brain cortical tissue prepared from an amyloid-bearing APP transgenic mouse in the presence of a chelator exhibit enhanced extraction of pelletable Aβ. (*See id.* at page 95, lines 16-18.)

A person of ordinary skill in the art, in view of the teachings of the specification, would have been able to practice the claimed methods of treating amyloidosis in a subject (claims 1 and 2), and would have been able to make and use the claimed pharmaceutical compositions (claim 37), without undue experimentation. The specification, for example, provides guidance as to the amount and timing of administration of chelators such as bathocuproine, (*see* Specification at page 45, lines 5-27) and possible modes of administration. (*See* Specification at page 46, line 8 through page 49, line 12.) In addition, persons of ordinary skill in the art would have been guided by the general teachings in the art relating to the formulation and administration of pharmaceutical compositions.

In order to establish a *prima facie* case of lack of enablement, the PTO has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants respectfully submit that the arguments set forth in the Office Action do not

constitute a "reasonable basis" for questioning the enablement of the present invention. Therefore, a *prima facie* case of non-enablement has not been established.

The Examiner, in support of the rejection, asserted that:

> The skilled artisan must resort to trial and error experimentation to determine the optimal quantity of bathocuproine/indomethacin to be administered, as well as the duration of treatment and route of administration. Such trial and error experimentation is considered undue.

(Paper No. 24, page 5.) Applicants note that quantity, duration of treatment and routes of administration are parameters that are routinely determined and optimized in the preparation/administration of any pharmaceutical composition. Moreover, the need for experimentation by itself is not sufficient to support a finding of non-enablement as long as the amount of experimentation is not regarded as undue. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *see also In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Examiner has not explained why making and using pharmaceutical compositions comprising bathocuproine would involve a greater amount of experimentation with respect to the determination of quantity, duration and routes of administration than is required for other compounds that have been routinely developed and administered effectively as pharmaceutical compositions in the art. There is no evidence to indicate that determining these parameters would be regarded as undue experimentation. Therefore, the alleged need for "trial and error experimentation" to determine quantity, duration and routes of administration of bathocuproine/indomethacin is not legally sufficient to support a *prima facie* case of non-enablement.

Applicants have previously asserted that the *in vitro* results presented in the specification, showing that bathocuproine is able to solubilize Aβ in human brain preparations, strongly suggests that bathocuproine would exert similar effects when administered to subjects suffering from amyloidosis. (*See* Applicants' Amendment and Reply Under 37 C.F.R. § 1.111, filed February 26, 2003 ("the February 26, 2003 response"), at pages 15-16.) It was also noted that there has been no evidence presented to explain why the *in vitro* results are not indicative of *in vivo* results. (*See id.*) In response, the Examiner stated that "the *in vitro* results obtained with bathocuproine may not necessarily be indicative of the results obtained with this metal chelator *in vivo*." (Paper No. 24, page 7.) To support this position, the Examiner first stated that the extraction of Aβ from the cortex of AD brains was significantly enhanced by the presence of TPEN, but that, according to Fonte *et al.*, *J. Alzheimer's Disease 3*:209-219 (2001) ("Fonte"), "TPEN is of limited benefit to patients because it is highly toxic."

The statement in Fonte regarding the toxicity of TPEN, however, does not support the conclusion that *in vitro* results for chelators are not indicative of *in vivo* results. First, there is no evidence in Fonte to indicate that TPEN, when administered to patients, would fail to promote Aβ solubilization as it did *in vitro*. Second, the statement in Fonte simply indicates that TPEN might be of "*limited* benefit" due to its toxicity. The assertion that the benefits of TPEN may be "limited" does not suggest that TPEN would be ineffective in solubilizing Aβ in the brains of AD patients. Third, the reference cited in Fonte to support the statement that TPEN is "highly toxic," *i.e.*, Adler *et al.*, *Toxicon. 35*:1089-1100 (1997), relates to the administration of TPEN to mice and states that "low doses of TPEN . . . were well tolerated." (*See* Adler, abstract, copy submitted herewith as exhibit 1.) Thus, it is

likely that reducing the dose of TPEN would avoid any toxicity issues while nonetheless promoting Aβ resolubilization *in vivo*.

The Examiner also made reference to the chelator desferrrioxamine (DFO), and noted that DFO was reported to significantly arrest the progression of AD. (*See* Paper No. 24, page 7, citing Cuajungco *et al.*, *Annals NY Acad. Sci. 290*:292-304 (2000) ("Cuajungco").) The Examiner cited Cuajungco for the propositions that: (a) "DFO is a charged molecule that does not easily penetrate the blood-brain barrier and is easily degraded after administration," and (b) "the administration of DFO is associated with discouraging difficulties including the nonspecific problems of systemic metal ion depletion and the problem of administration of a twice-daily, painful intramuscular injection." (*See* Paper No. 24, page 7.)

First, it is unclear how the Examiner's statements regarding DFO support the assertion that *in vitro* results with chelators do not necessarily reflect *in vivo* results. That is, the Examiner has not cited any *in vitro* results with DFO to which *in vivo* results may be compared. Second, the *in vivo* results with DFO cannot reasonably be used to predict the *in vivo* results with bathocuproine because, while DFO is a "highly charged molecule," bathocuproine is non-polar. Third, the supposed difficulties associated with DFO actually support the conclusion that administration of chelators would not involve undue experimentation. Even though DFO supposedly causes "systemic metal ion depletion" and is administered by "painful intramuscular injection," it is clear that DFO is nonetheless effective at arresting the progression of Alzheimer's disease. Persons of ordinary skill in the art clearly were able to formulate and administer DFO in an effective manner notwithstanding the technical difficulties associated with this chelator. Thus, surmounting

the potential technical difficulties associated with chelators (such as systemic ion depletion and effective route of administration) cannot be regarded as undue experimentation. The results from studies with DFO therefore do not support the position that the *in vitro* results obtained with bathocuproine may not be indicative of the *in vivo* results obtained with this chelator.

The Examiner also stated that "there are several important points that must be taken into consideration before and during the administration of a metal chelator to a subject." (*See* Paper No. 24, page 8.) The Examiner cited Gnjec *et al.*, *Frontiers Biosci. 7*:1016-1023 (2002) ("Gnjec") which discusses certain technical considerations associated with chelator therapy. There is no evidence, however, to suggest that such considerations would amount to undue experimentation. The fact that chelators such as DFO and clioquinol (*see* discussion below) have been formulated into pharmaceutical compositions and have been successfully administered to subjects, thereby causing cognitive improvements in patients with Alzheimer's disease, indicates that addressing the technical considerations set forth in Gnjec can be accomplished using routine methods in the art and would not be regarded as undue experimentation.

Applicants have previously cited the positive results obtained with the metal chelator clioquinol to support the position that *in vitro* results with metal chelators are reliable indicators of *in vivo* results. (*See* the February 26, 2003 response at pages 16-17.) Briefly, it was noted that clioquinol, like bathocuproine, was first shown to promote the solubilization of Aβ *in vitro*, and that clioquinol has since been shown to effectively inhibit brain Aβ deposition when administered to a transgenic mouse model of Alzheimer's disease and to improve cognitive parameters and blood levels of Aβ when administered to humans.

(*See id.*) Since the *in vitro* results involving clioquinol accurately reflected the results obtained *in vivo*, *i.e.*, the treatment of amyloidosis in subjects, it is reasonable to conclude that a similar progression (*i.e.*, from *in vitro* data to *in vivo* results) would have been achieved using bathocuproine without undue experimentation.

The Examiner has not presented any evidence or scientifically sound reasoning to indicate that the success obtained with clioquinol would not have also been achieved with bathocuproine. The Examiner simply stated that clioquinol is specific for copper and zinc ions and has a different chemical make-up and structure than bathocuproine, which is specific for copper. (*See* Paper No. 24, page 9). Whether or not clioquinol differs from bathocuproine at the chemical level, the fact remains that persons of ordinary skill in the art were clearly able to formulate and administer metal chelators to subjects for therapeutic purposes without undue experimentation.

Moreover, the burden of establishing a *prima facie* case of non-enablement falls on the Examiner; it is not Applicants' burden to initially establish that the invention *is* enabled. *See Wright*, 999 F.2d at 1561-62, 27 USPQ2d at 1513. To establish a *prima facie* case of non-enablement, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). The results obtained with clioquinol demonstrate that, based on *in vitro* results using the same or similar assay systems as those described in the present application, persons of ordinary skill in the art were able to successfully administer clioquinol in *in vivo* animal models and ultimately in human clinical trials without undue

experimentation. Since, in the case of clioquinol, it was within the expertise of the skilled artisan to develop an appropriate dosage and dosage regimen for the effective administration of this chelator, it follows that it would have also been within the expertise of the skilled artisan to do the same with bathocuproine, regardless of how similar or different clioquinol is to bathocuproine. No evidence has been presented to suggest that this is not the case.

Finally, Applicants maintain that the passage in Gillmore *et al.*, *Brit. J. Haematol. 99*:245-256 (1997) ("Gillmore"), which was cited by the Examiner in Paper No. 21, page 5, merely indicates that, at the time of this reference, research in the area of amyloid deposit mobilization was *ongoing*. The fact that others in the art had not been able to accomplish the results provided by the present invention cannot form the basis for a proper enablement rejection. *See Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). Thus, the statements in Gillmore do not support a *prima facie* case of non-enablement.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1 and 2 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*See* Paper No. 24, page 11.) The Examiner noted that claim 1 recites "said chelator" but that there is insufficient antecedent basis for this phrase. Claim 1 has been amended to replace "said chelator" with "said bathocuproine or

hydrophobic derivative thereof." In view of this amendment, the rejection under 35 U.S.C. § 112, second paragraph, has been fully accommodated and should be withdrawn.

V. Claim Rejections Under 35 U.S.C. § 103

Claim 37 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Sigma Chemical Company catalog number B 1000, page 149 (1995) in view of Goodman and Gilman, "The Pharmacological Basis of Therapeutics," New York: McGraw-Hill, Inc., pages 5-6 (1993). (*See* Paper No. 24, page 11.) Applicants respectfully traverse this rejection for the reasons set forth in the February 26, 2003 response at pages 23-25.

Nonetheless, solely to expedite prosecution, claim 37 has been amended to include the limitation found in claim 38 (now cancelled). Claim 38 was not rejected under 35 U.S.C. § 103. Therefore, the rejection under 35 U.S.C. § 103 has been fully accommodated and should be withdrawn.

VI. U.S. Patent No. 6,022,879

Applicants have recently become aware of U.S. Patent No. 6,022,879 to Crow *et al.* ("Crow"), a copy of which is submitted herewith as Exhibit 2. Crow issued on February 8, 2000 from U.S. Patent Application No. 09/173,105, filed October 15, 1998, which claims the benefit of U.S. Provisional Patent Application No. 60/062,428, filed October 15, 1997. The earliest effective filing date of the present application is March 11, 1997. Thus, Crow is not prior art with respect to the present application.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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EXHIBIT 1

1: Toxicon. 1997 Jul;35(7):1089-100.

Protection by the heavy metal chelator N,N,N',N'-tetrakis (2-pyridylmethyl) ethylenediamine (TPEN) against the lethal action of botulinum neurotoxin A and B.

Adler M, Dinterman RE, Wannemacher RW.

Neurotoxicology Branch, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD 21010-5425, USA.

The ability of N,N,N',N'-tetrakis (2-pyridylmethyl)-ethyenediamine (TPEN) to protect against botulinum neurotoxin (BoNT) A and B was examined in vivo in mice. To determine the protective efficacy of TPEN, mice were injected i.p. with TPEN as a single bolus or as multiple injections 30 min before and 0, 2, 4 and 6 hr following i.v. challenges with BoNT-A or -B. TPEN treatment did not alter the 24 hr lethality of BoNT but did produce a significant delay in the time to death. For a moderate dose of serotype A (20 LD50), five divided doses of TPEN prolonged the time to death from 7.8 +/- 0.4 hr to 9.9 +/- 0.5 hr. For serotype B, examined under comparable conditions, the prolongation of the time to death was from 6.1 +/- 0.2 hr to 9.4 +/- 0.6 hr. The range of TPEN doses that could be examined in vivo was limited by its acute toxicity. Although low doses of TPEN (< or = 10 mg/kg) were well tolerated, higher doses (> or = 30 mg/kg) led to ataxia, loss of coordination, convulsions and death in 20.3 min or less. In clonal NG108-15 cells, TPEN was found to produce cytotoxicity as revealed by increases in the secretion of the marker enzyme lactate dehydrogenase (LDH), and enhanced reactivity with the vital dye trypan blue. From LDH concentration-response data determined 24 hr after addition of TPEN, the threshold concentration for observing cytotoxicity was 10 microM and the IC50 was 19.8 microM. At the highest TPEN concentration tested (100 microM), cytotoxicity was detected 8 hr after TPEN addition and increased in severity over a 3 day period. The cytotoxicity in NG108-15 cells appears to be distinct from the rapid-onset toxicity observed in whole animals. These results suggest that TPEN may be of potential benefit in delaying the lethal actions of BoNT-A and -B, but its use is limited by its initial and delayed toxicity. Since the therapeutic and toxic actions of TPEN are both related to zinc chelation, the use of TPEN would need to be restricted to low doses as part of a combination therapy.

PMID: 9248007 [PubMed - indexed for MEDLINE]

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EXHIBIT 2

US006022879A

United States Patent [19]

Crow et al.

[11] Patent Number: 6,022,879

[45] Date of Patent: Feb. 8, 2000

[54] **BATHOCUPROINE TREATMENT OF NEUROLOGIC DISEASE**

[75] Inventors: **John P. Crow; Joseph S. Beckman**, both of Birmingham, Ala.

[73] Assignee: **UAB Research Foundation**, Birmingham, Ala.

[21] Appl. No.: **09/173,105**

[22] Filed: **Oct. 15, 1998**

Related U.S. Application Data

[60] Provisional application No. 60/062,428, Oct. 15, 1997.

[51] **Int. Cl.**[7] **A61K 31/445**

[52] **U.S. Cl.** **514/319**; 514/320; 514/321

[58] **Field of Search** 514/319, 320, 514/321

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,834,457 11/1998 Bredesen et al. 514/188

OTHER PUBLICATIONS

Ghadge et al., "Mutant superoxide dismutase-1-linked familial amyotrophic lateral sclerosis:molecular mechanisms of neuronal death and protection", J. Neurosci. (1997), 17(22), pp. 8756–8766 (abstract).

Primary Examiner—Kevin E. Weddington
Attorney, Agent, or Firm—Benjamin Aaron Adler

[57] **ABSTRACT**

The present invention provides a method of treating amyotrophic lateral sclerosis and other neurologic diseases by administering bathocuproine or a related analog. Also provided are pharmaceutical compositions of bathocuproine.

11 Claims, 33 Drawing Sheets